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Dr. Andre DeLean, M.D., Ph.D.
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Dear Dr. DeLean:

Thanks very much for the letter and the pre-print of your forthcoming paper on the modeling of the binding of agonists and antagonists to the beta adrenergic receptor. I enjoyed reading the paper both with respect to style and content. As you might have guessed from my public comments at the Brussels meeting, I also dabbleⁱⁿ models and modeling but do not take the latter approach too seriously any longer mainly because of the numerous assumptions that need to be considered in the case of adenylate cyclase systems. Nonetheless, I do appreciate the efforts made, otherwise we would not have spent so much time on this approach in the past. We did not model the binding of hormones to receptors. Early findings with the glucagon receptor indicated that its binding must be more complex than a "simple" biomolecular process because of the slowness of the process to reach "equilibrium" and the fact that guanine nucleotides alter the binding of the hormone. Our explanation is that the hormone binds to an RN (your RX) complex which can take differing forms (polymeric, monomeric, and linked to the effector, C). As viewed in my recent Nature article, this explanation is consistent with various biochemical data obtained from a number of cyclase systems reported in the literature. Its virtue^{is} its predictive quality. However, as with any "good" theory, it requires the best experimental evidence to prove that it is incorrect or inadequate. Thus far, I am satisfied with its adequacy. If one accepts the assumptions in your model, we both agree that an RN (RX) complex can pre-exist in the membrane of the frog erythrocyte. Apparently, you are disturbed by our evidence that RN exists in the form of oligomers. However, since RX (or RN) can pre-exist in the membrane of the frog erythrocyte as a complex one need not be disturbed if it is made up of multiple RN (or even RNC) units. This finding does not upset your model which suggests that the hormone "stabilizes" the RN complex (polymeric or not). That is our interpretation of the solubilization studies of Limbird. In a recent letter from her, she seemed to agree that

this is a valid interpretation. At this point, however, it is necessary to establish by independent criteria whether the RN complex pre-exists in the membrane as a complex and that the complex may be an aggregate. These are some of our research goals. Target analysis has the limitation (as do all sizing techniques) of not yielding information on the components that make up the functional unit which is being measured. Minimally, the cyclase system is made up of R, N, and C. However, we now think that R, N, and C, are each composed of more than one type of molecule. Target analysis of the turkey erythrocyte system (submitted for publication) indicates that R and N are pre-associated in the membrane with the catalytic unit and that the regulatory complex (RN) probably consists of heterologous or homologous subunits. From what we learned at Brussels, I am convinced more than ever of the heterogeneity of molecular species comprising N (or G, or G/F).

Now to the substance of your letter, which is to suggest some form of collaboration involving the use of target analysis. In principle, I favor such a collaboration. Limbird recently asked whether we could collaborate with her using the reticulocyte cyclase system which she thinks is the most suitable system for evaluating the behaviour of the beta adrenergic receptor. You suggest that the frog erythrocyte would be a good model system. Unfortunately, the amount of work necessary even for one system is horrendous and would require a number of man-hours of work. Thus, I believe that only one system need to be evaluated, particularly since we have already consumed a great deal of effort on the turkey erythrocyte beta adrenergic system. Perhaps the three groups (yours, Limbird, and ours) should get together at NIH in October (I suggest around the 15th) to discuss the best approach and what can be gained by studying these systems in detail. As you know, I leave for Dallas in November. However, Dermot Cooper and Sue Preston could, with Ellis Kempner, carry out parts of the work at NIH while you and Limbird may wish to take differing analytical aspects of the problem in your respective laboratories. We could send the frozen, irradiated samples to each of you for processing (binding, cyclase) while Cooper and Preston could carry out the incubations prior to irradiation.

So, I look forward to your reply and a date that would be agreeable for getting together, preferably in October but even at a later date if October should prove difficult. I will be gone from the lab during September. I suggest that you call Dermot Cooper (301-496-6991) and discuss the issue directly with him.

Au revoir.

Sincerely,



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